OPEN ACCESS Freely available online

Research Article

American Journal of Clinical and Medical Research

Advances In Polymer Nanoparticles: A Strategy for Developing Nanocarriers for Drug Delivery

Onome Ejeromedoghene[a*], Abiodun Oladipo[b], George Egejuru[c]

[a] School of Chemistry and Chemical Engineering, Southeast University, Jiangning District, Nanjing, Jiangsu Province, 211189, PR China
[b] Co-Innovation Center for Sustainable Forestry in Southern China, College of Forestry, Nanjing Forestry University, 210037 Nanjing, Jiangsu, China.
[c] School of Public Health, Southeast University, Jiangning District, Nanjing, Jiangsu Province, 211189, PR China

***Corresponding author:** Onome Ejeromedoghene, School of Chemistry and Chemical Engineering, Southeast University, Jiangning District, Nanjing, Jiangsu Province, 211189, PR China. Tel.: +86-18851663211

Citation: Ejeromedoghene O, Oladipo A, Egejuru G (2022) Advances In Polymer Nanoparticles: A Strategy for Developing Nanocarriers for Drug Delivery. Ameri J Clini Medi Re: AJCMR- 104.

Received Date: 20 November, 2022; **Accepted Date:** 30 November, 2022; **Published Date:** 05 December, 2022

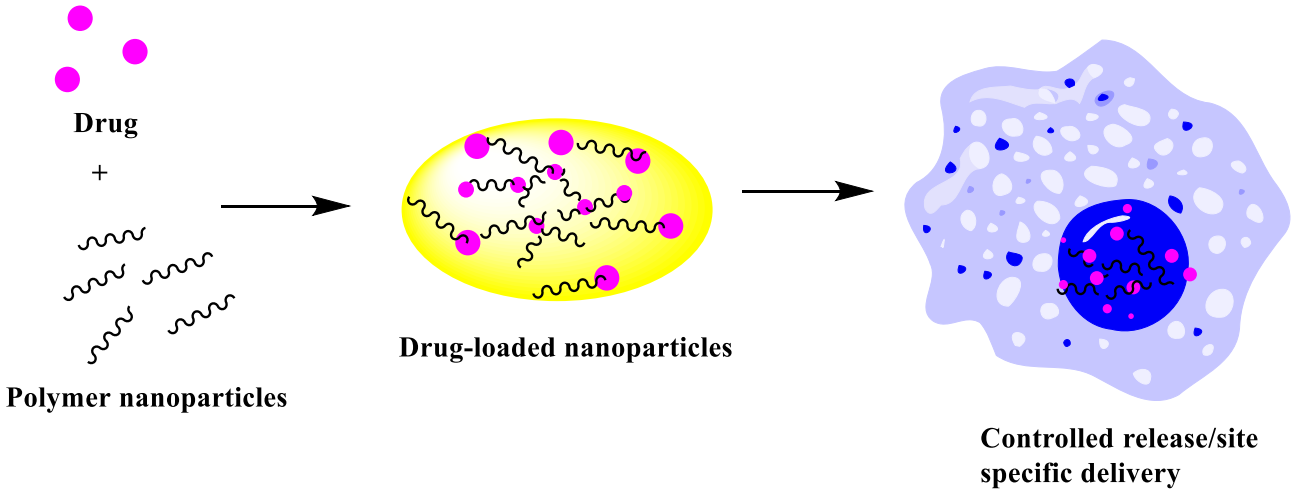
Abstract

With the ever-increasing proliferation of disease-causing organisms and illnesses, disease therapy has shifted its focus to correctly targeted dosage forms of drug administration. Over the years a lot of fascinating achievements have been made in the management of disease through the invention of drug delivery. But conventional drug delivery systems are often faced with low solubility and permeation of drug molecules as well as chronic side effects and complications due to their wide distribution throughout the body fluids. The main objective of the target delivery of drugs is to achieve a desired pharmacological response at a pre-determined site without undesirable interference at other sites. Thus, the recent advancement in nanomedicine has open numerous avenues for the site-specific and controlled release of therapeutic drug agents. Polymer nanoparticles, like other nano-particulate materials, are characterized as excellent drug delivery vehicles owing to their uniform size control, longer clearance time, biodegradability, biocompatibility, increased therapeutic efficacy, and lower toxicity. This review highlights the advances in the preparation and application of some polymer nanoparticles as drug delivery vehicles in biological systems with little or no associated health risks.

Keywords: *Polymer nanoparticles, Drug delivery, Controlled release, Drug loading, Nanomedicine.*

Graphical Abstract

Polymer nanoparticles, like other nano-particulate materials, are characterized as excellent drug delivery vehicles owing to their uniform size control, longer clearance time, biodegradability, biocompatibility, increased therapeutic efficacy, and lower toxicity.



Introduction

The advancement in scientific research has led to the discovery of new drugs for specific disease-causing microorganisms. Low solubility and penetration of some of these therapeutic compounds through biological barriers in the body system, on the other hand, has proven difficult, thereby resulting in unnecessary delays in delivering the active ingredient to the target regions. In addition, errors in using regular drugs reduce the compliance of the patient, typical peak–valley plasma concentration-time profile, and high peak; an example of such is the repetition in administering medications with a shorter half-life. This has constituted a serious challenge in specific target delivery and balanced concentration of medications [1]. Besides, the development of new systems for the delivery and release of drug molecules targeted at tissues, organs, or damaged cells has been presented in nano-medical science. This new system capitalizes on the causative microbe by knowledge of their pathological, physiological, and mutational characteristics [2,3].

Nanoparticles are known for their high encapsulation capacity, biocompatibility, fashionable functional features, high surface charge/area-volume ratio and minute sizes range from 1-100 nm amongst others. The green or biological synthesis of nanoparticles based on phytochemicals from numerous plant extracts empowers nanoparticles to function effectively as drug carriers without toxicity concerns. Compared to typical macroscale drug delivery equivalents that present certain loopholes such as drug resistance, side effects owing to high dosage, treatment failure, and high cost. Nano-medication also poses little or no danger due to its unique characteristics. Although there are some safety concerns and ethical issues with regards to the application of nano-formulations, the morphological changes arising from the tunable shapes and sizes of these materials can magnificently affect their physical and chemical transformations in the cells, tissues, or organs, thereby producing the required results [4]. More specifically, as powerful nano-carriers of hydrophilic and hydrophobic medicines, nanoparticles made of biodegradable polymeric materials have contributed tremendously in the furtherance of drug delivery technology i.e. they can be delivered in the needed dosage to specified target areas or cell populations in biological systems in a preset manner, and they disintegrate in a reasonable amount of time [5–8]. Nevertheless, DNA which is generally known to carry hereditary information can be explored as a binding template, where it provides a platform for metal nanoparticles to attach to its surface [9,10]. As a result, drug-loaded nanoparticles can encapsulate and distribute medications in a unique style especially when provided with a pharmacokinetic profile, resulting in better therapeutic efficacy when compared to traditional treatments that rely on basic pharmaceuticals alone.

General Overview

Nanocarriers

The submicron particle size of nano-carriers is reported to be < 200 nm and about 1–1000 nm in diameter [11]. Due to the small size and large surface area they possess, they have attracted a lot of interest as drug delivery vehicles in biological systems. The successful delivery of bioactive drugs to specific sites that appears to be difficult to access around the body is made possible with little or zero toxicity, targeted delivery to specific sites, improved solubility, and systematic release by drug encapsulation through the help of nano-carriers [12,13].

The importance of nano-carrier in the delivery process of medication to specific cells/organs is attributed to their specialized ability to pilot medication to the targeted site with highly successful accuracy. Significantly, the accuracy at which the infected site is targeted is a therapeutic advantage since it prevents the wrong administration of medications to inappropriate locations [14]. Nano-carriers also have the potential for application in chemotherapy because they can help reduce chemotherapy's deleterious effect on healthy cells that are fast-growing on a broader scale throughout the body system. Where chemotherapeutic drugs are programmed for specific parts, delivery to other body tissues can be exceedingly damaging to human cells [15]. Nano-carriers are known to deliver medications by employing four basic methods, namely, passive targeting temperature specificity, pH specificity, and active targeting

Passive targeting

In passive targeting, the nano-carrier proceed to the vascular system of a tumor where it becomes trapped and piles up in the tumor area. The exterior of most nano-carriers is coated with poly(ethylene oxide) (PEO) which is known to improve penetration and reservation [16,17]. PEO permits nano-carriers to pass through a tumor's leaky vasculature, preventing them from escaping. Certain tumors with penetrable vascular tissue have been linked with the presence of very small pores and tumors with blood vessel development. The entrance of nano-carriers is possible through the pores, but they also contain multiple bends that trap the nano-carriers. The medication accumulates at the tumor location as more nano-carriers become trapped [18]. Large quantities of the medicine are given directly to the disease site because of this build-up. The negative effect of PEO on the association with cell-nanocarrier is observed because many nano-carriers must be absorbed into the cells before the medications can be released.

Active targeting

Active targeting entails placing targeting modules on the exterior of nano-carriers with uniqueness to different cells present in the human system, such as ligands or antibodies. Since the surface area-to-volume ratio of nano-carriers is large, it provides the opportunity to accommodate numerous ligands on their surfaces [19].

The fusion of nano-carriers with cells is made possible in a specialized manner, although they come with significant disadvantages. Due to the non-specific binding, ligands may cause nano-carriers to be slightly more hazardous, thereby causing the efficiency to deliver medications inside cells to be hindered by positive charges on ligands. In some tumor cells, the battle against multidrug resistance could be won by active targeting [20].

pH Specificity

In some medications, the efficiency of nano-carriers to release their content in a biological system can only be achieved at a certain range of pH. Therefore, the use of pH specificity could be integrated into nano-carriers targeted at the direct supply of medications to the site where the disease is located. In particular, the normal tissue was reported to have a pH of about 6.8, however, tumors are known to be largely more acidic than normal human cells. [16]. Nano-carriers that exclusively release medications at specific pH ranges can thus be utilized to deliver drugs solely to acidic tumors sites [18]. Structural degradation of nano-carriers is responsible for the medication release especially in highly acidic areas [21]. The introduction of copolymer chains to micelles that performs without pH can generate sensitivity of pH in micelle systems. These micelle-polymer complexes also aid in the prevention of multi-drug resistance in some cells. Based on the low pH, the polymerized micelle can be released in a short time, thereby leading to the deposition of a greater part of the medication alongside other pharmacological treatments almost at the same time instead of a gradual release [17].

Temperature Specificity

At certain temperatures, some nano-carriers have also been demonstrated to transport medications more effectively. Since tumor temperatures are typically higher compared with the temperatures of other body parts, about 40 °C, the gradient in temperature helps to protect tumor-specific site delivery [15].

Polymer Nanoparticles

Polymer nanoparticles are designed to be flexible biomaterials with an easy method for production and a structure that can be easily altered to create the necessary features and tunability to enhance delivery or medication performance. The bio-distribution and therapeutic efficacy of polymer nanoparticles could be improved due to their biocompatibility and also their biodegradable nature in many systems with nanoscale proportions [22]. Many medicinal compounds have been developed using polymer nanoparticles derived from natural sources such as chitosan, collagen, gelatin, and dextran, lectins, poly(aminoacids), poly(ethylene glycols), and others [23,24]; as well as biodegradable synthetic polymers which include poly (lactic acid) (PLA), poly (glycolic acid) (PGA), poly(-caprolactone) (PCL), poly (styrene-maleic anhydride) copolymer, and polyamide-amine (PAMAM) dendrimers, etc. [25–27]. By employing a polymeric matrix mechanism, medication can be encased during formulation development, or by attaching molecules of polymers for an adjusted target to active location [28].

Furthermore, the flexibility and biodegradability of nanoparticles is a key reason why they are employed as polymer nano-carriers; it is also possible to prepare them in different forms; thus, their usability in the release of enveloped proteins, peptides, DNA and RNA and medication that are either soluble or insoluble in water, which are all types of biomolecules. Importantly, to ensure the bio-distribution of particles in the body of a human, the size of polymer nano-carriers usually ranges from 10 to 200 nm. Also, it should be noted that stabilization and dispersion of polymer nano-carriers should be organized in such a way that ionic strength, polarity, pH, or temperature in *in vivo* or physiological environments are not affected [29].

Designing Polymer Nanoparticles

Polymer nanoparticle breakdown is an essential aspect necessary for the advancement of material science and nanomedicine as the novel material combines the outstanding features of both nanocomposites and polymers [30] i.e. the polymer matrix can act as stabilizers/capping agents that prevent aggregation, agglomeration, and impact uniform size distribution when producing metal nanoparticles. The selection of the drug and the polymer is critical in drug delivery; similarly, the method of preparation is critical in acquiring the desired properties [1]. Polymer nanoparticles are made from a wide variety of polymers. Natural polymers extracted from plant products and animal wastes can be effectively utilized for fabricating polymer nanoparticles because they can perform the dual functions of capping and reduction (**Figure 1**). The combination of various polymeric systems with nanostructures has aided in the development of a sustained-release drug delivery system.

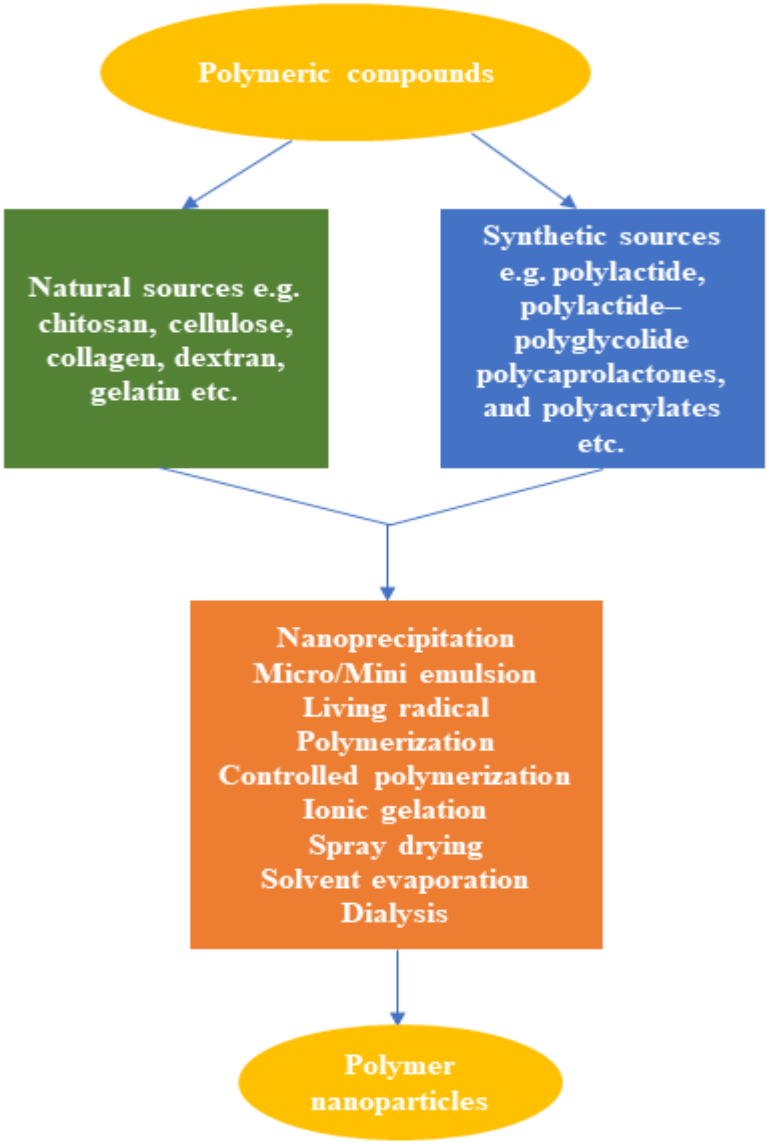


Figure 1: Overview of polymerization approaches for the preparation of polymeric nanoparticles

The technology of nanoparticle preparation, on the other hand, has seen several breakthroughs. In recent years, numerous new innovative and novel approaches for the creation of polymeric nanoparticles have evolved. Fidalgo et al. [31] for example, used the soft sol-gel technique to fabricate a nano-hybrid silica/polymer aerogel monolith that was dried at ambient pressure; of which the diameter was within 32 to 132 nm. With the aid of two consecutive orders of acid/basic catalytic breakdown of chemicals which are soluble in water and the principle of co-condensation, it was possible to produce the hybrid polymer nanoparticle interconnected nanoparticles of poly (butyl methacrylate-co-butyl acrylate) having groups of trimethoxysilyl-functionalized poly(butyl methacrylate) when the core and core-shell morphologies are considered. In an experiment conducted by Smyth et al. [32], based on PEG-based oligo(ethylene glycol) methacrylate (OEGMA). The authors assembled benzaldehyde-functionalized amphiphilic block copolymers; also, by using reversible addition-fragmentation chain transfer (RAFT) polymerization they were able to prepare pH-responsive 2-(diisopropyl)aminoethyl methacrylate (DPA) monomers and benzaldehyde-containing para-formyl phenyl methacrylate (pFPMA). The pH-responsive and biocompatible polymeric nanoparticles with diameters of 180–230 nm were completely absorbed in an *in vitro* trial for A2780 ovarian cancer and A549 lung epithelial human cells. Based on the solvent displacement approach, Karimi et al. [33] successfully grafted all-trans retinoic acid (ATRA) onto poly β-amino ester (ATRA-g-PBAE copolymer) and applied it for the encapsulation of docetaxel (DTX), towards the fabrication of DTX loaded ATRA-gPBAE nanoparticles. The nanoparticles with an optimum size of 137.9 ± 2.09 nm showed an increase in cytotoxicity and anti-angiogenic activity than that of free ATRA and DTX in an *in vitro* release system for chemotherapeutic applications. Insulin loaded with poly (n-butylcyanoacrylate) nanoparticles (Ins/PBCA NPs) were polymerized by Cheng et al. [34]. The nano-carrier was also n-butylcyanoacrylate (BCA). When in gastric fluid, the stability of nanoparticles was observed and it was released inside the intestine in a controlled manner, with the release rate increasing as the insulin/BCA mass ratio increased.

Application of polymer nanoparticles as drug delivery vehicles in various fields of nanomedicine

The advent of nano-medicine has resulted in the discovery of a plethora of innovative materials that have been used to treat a variety of human ailments. Some recent applications of polymer nanoparticles are hereby highlighted below.

Therapeutic Agents

The usability of nanoparticles from polymers in therapy covers numerous disease therapy. For instance, Alves Batista et al. [35] in an experiment described the synthesis of poly(methyl methacrylate) (PMMA) by encapsulating α-terpineol through the mini-emulsion technique. The safety in pharmaceutical use of PMMA that was prepared with 400 mg of -terpineol experimented in erythrocytes, cells of animals which are normal like macrophages and fibroblasts (MRC-5) and Artemia salina (LC50 698.8 74.6, 24 h incubation) was confirmed by the profile of its toxicology. The presence of 400 mg of -terpineol (5–500 g/mL) in PMMA when tested against mice melanoma cells (B16-F10) and humans (SK-MEL-28), indicates that these nanoparticles could be used to treat melanoma. Sohail and Abbas [36] formulated alginate–chitosan nanoparticles (ACNPs) and studied their potential as agents for drug delivery for amygdalin encapsulation targeted at cancer cells. To learn more about how the medication delivery and cell toxicity are affected by charge, the researchers created ACNPs loaded with Amygdalin having outer layers that consist of both anion and cation. When tested for mucoadhesion, attachment of ACNPs to porcine mucin-type II was successful and transmigrated through a channel under a bio-impersonated flow system without any coating at an average velocity of 1.68 m/s. In a dose-dependent way, ACNPs appeared to prolong the anti-cancerous effect but were stronger than free amygdalin on the lines of the H1299 cell, implying that the former has a higher cellular absorption. Also, Thakur and colleagues [37] used the process of dual emulsion solvent evaporation to study the production of nanoparticles having a size of 213.8 ± 2.5 nm, the efficiency of encapsulation of 52.24 ± 3.1 %, and flexible shape from carboplatin-loaded ethyl cellulose. The hydrogel's anti-tumor activity was also demonstrated in the Ehrlich ascitic carcinoma mouse model. The sustenance of the medication release was well-managed for 7 d (94.53 ± 0.91 %) with improved nanoparticles implanted within the *in situ* hydrogels; while non-nanoparticle commercialized medications were released in about 2 h. External (hemolysis and cytotoxicity) and internal toxicity studies revealed that the developed hydrogel was safer and more tolerable than the commercially available materials. Using a single-step crosslink of branched poly(ethylenimine)-g-methoxy poly(ethylene glycol) copolymer (PEI-g-mPEG) with hydrophobic terephthalaldehyde (TPA) molecules at pH 7.4 aqueous solution, it was possible to develop nanogels from functionalized polymer with pH-responsive benzoic-imine cross-connected as carriers for indocyanine green (ICG) delivery (**Figure 2**) [38]. A greater amount of TPA molecules were interconnected with PEI-g-mPEG segments which generated the development of micro-domains in greater percentage within nanogels polymer, and as a result, the compatibility and hydrophobicity of the colloidal structure increased. More importantly, by employing the amphiphilic ICG molecules through electrostatic attraction with protonated PEI segments, the encapsulation of the ICG species into the nanogels can be well optimized, and upon π - π stacking their hydrophobic association with micro-domains can be improved too. The robust ICG-loaded nanogels demonstrated several noteworthy features which include the following; (1) the improvement in phosphate buffer of ICG photo-stability significantly, (2) significant delay of ICG outflow at a pH of 7.8 from nanogels (3) when responding to the decrease in pH to 6.4 from 7.8, acid-triggered ICG by connection to benzoic-imine bonds are released. Additionally, Pramual and colleagues developed [39] photodynamic therapy (NPs/PDT) using a nanoparticle-mediated mechanism to subdue multidrug resistance (MDR) and cancer cell spread (metastasis). This was possible because the PLGA-lipid hybrid nanoparticles were loaded with a photosensitizer, 5,10,15,20-Tetrakis(4-hydroxy-phenyl)-21H,23H-porphine (pTHPP). The nanoparticles photo-cytotoxicity nanoparticles were examined by considering two distinct models of MDR. The development of these models from A549 human lung adenocarcinoma of one cell line to include (1) developed MDR which is a derivative of A549 cells through selective medication known as A549RT-eto, (2) the procurement of MDR whose detachment was necessitated by A549 cells as seen in non-connected conditions when cultured in floating cells, imitating in blood or lymphatic circulation the nature of metastasizing cancer cells. When compared to A549 parental cells in the MDR model for drug selection, the resistance revealed by A549RT-eto cells and paclitaxel etoposide was reported to be 1.8 and 17.4 -fold respectively. The photocytotoxic effect in A549RT-eto and parental cells appear similar in NPs/PDT with pTHPP-loaded nanoparticles which are the opposite with anticancer medicines treatment. The intercellular levels of pTHPP accumulation and light-induced superoxide anion production of the two cell lines were similar. NPs/PDT by apoptosis through flow cytometry eradicated parental cells and A549RT-eto. It appears that A549 floating cells were more resistant to Etoposide (11.6-fold) and Paclitaxel (57.8-fold) in comparison to A549 attached cells, however, NPs/PDT photocytotoxic effect exhibited no resistance. It is the primary responsibility of the ability of PLGA-lipid hybrid nanoparticles to deliver the MDR-overcoming activity of NPs/PDT.

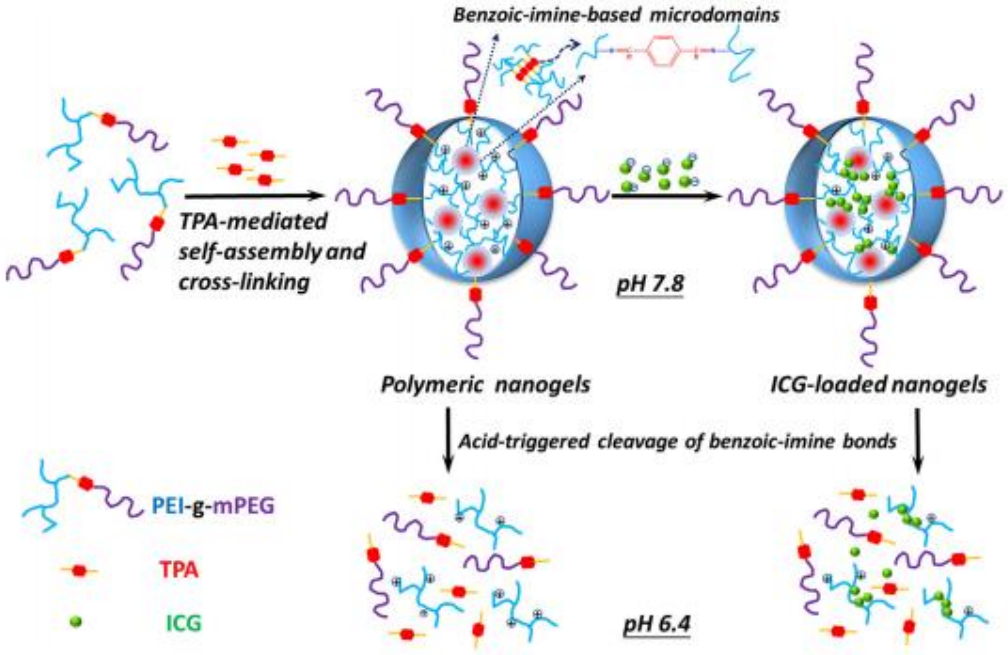


Figure 2: Illustration of the development of pH-responsive ICG-loaded polymeric nanogels for controlled ICG release. Reproduced from [38] Copyrights 2019 Elsevier Inc.

Gene Delivery Therapy

Exogenously modifying the genomes of cells to either stop the formation of defective proteins, introduce appropriately functioning sequences, or silence produced mRNAs is referred to as gene therapy. *In vitro*, gene therapy has shown to be quite effective, and it comes in a variety of forms, including siRNA, microRNA, mRNA, plasmids, and the most recently described CRISPR genome editing complexes [40,41]. Li et al. [42] offer a polymeric nanoparticle system that envelops negatively charged polymer/nucleic acid complexes to works as a medication depot, allowing for improved conservation and delayed gene payload delivery in the advancement of polymer nanoparticles in gene delivery therapy. Self-assembly was used to make the system out of biodegradable and biocompatible polymers. DNA plasmid-encoded with a green fluorescent protein (GFP) was employed as a reporter gene in Hek 293; the NPs demonstrated good cellular biocompatibility and gene delivery effectiveness (over 8 days). Over time, the nanoparticle-mediated continuous release of pGFP results in increased GFP expression. Jia et al. [43] developed a new inflammatory self-adaptive nano-carrier by forming a phenylboronate link between ascorbyl palmitate (AP) and the exterior of polymer nano-complexes that captured with gene. *In vitro* and *in vivo* studies show that adding AP to the mix boosts the concentration of imprisoned genes in inflammation and makes it easier for gene-loading nanoparticles to get into the cells (**Figure 3**). Memari et al. [44] also investigated the effectiveness of transfection of U87 cells with miR-128-encoding plasmid utilizing Poly(3-hydroxybutyrate)-co-polyethylenimine (PHB-co-PEI) nanoparticles generated by copolymerization, as well as the influence of this microRNA on U87 cell survival. The nanoparticles had an average diameter of 84.53 nm and zeta potential of 5.43 mV. It was revealed through the flow cytometry that there was no effect of nanoparticles on the apoptosis and necrosis of U87 cells, whereas nanoparticles loaded with a miR-128-encoding plasmid caused 24.5 % death of cells. Fluorescence microscopy and flow cytometry were used to assess the transfection effectiveness of PHB-co-PEI nanoparticles, which revealed that 7.48 percent of U87 cells were positive for green fluorescent protein (GFP) at a weight ratio of 40.

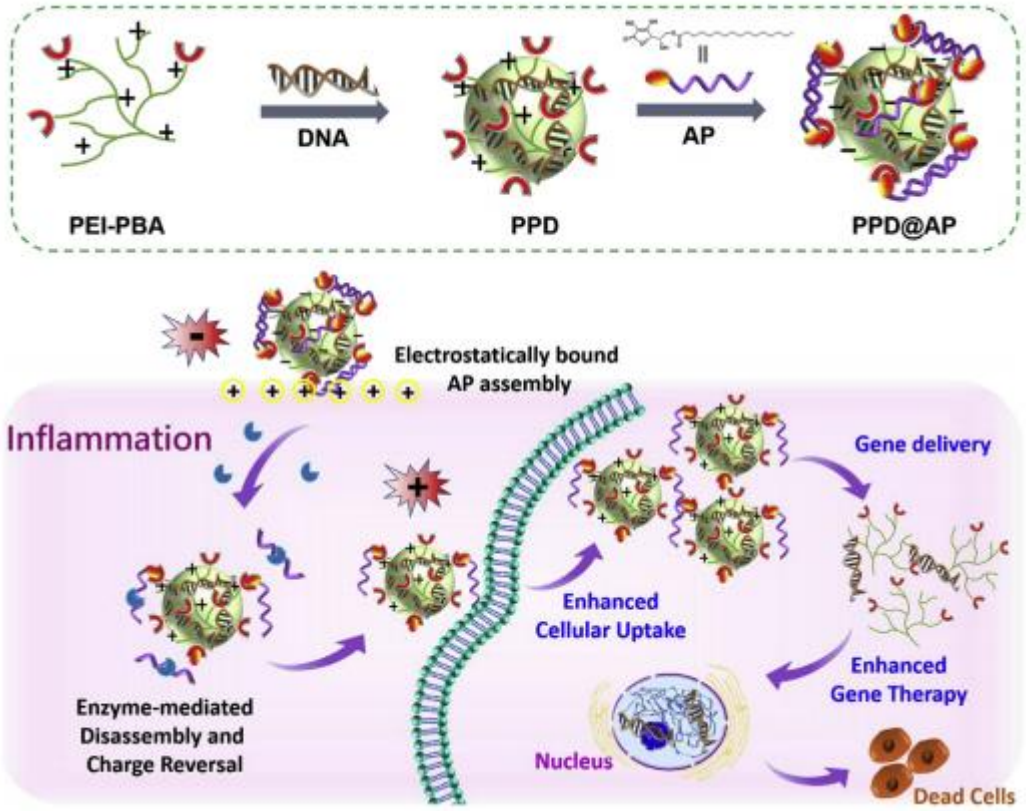


Figure 3: Coating exterior of PPD as formed phenylboronate bond in the development of inflamed self-adaptive nanocarrier (PPD@AP) and schematic illustration of PPD@AP as a nanoplatform to better the movement of cells and upgrade gene transfection efficacy for charge rearrangement in inflammatory microenvironment mediated by an enzyme. Reproduced from [43] Copyrights 2020 Elsevier Ltd.

Skin Permeation/Wound Healing

Due to the stratum corneum layer, which functions as a permeation barrier, the human skin plays an important defensive role. Cutaneous injury is a huge problem for the global health care system since any damage to the skin's protective layer, whether from wounds or burns, causes the skin to lose its protective role [45]. Several ideas have been offered to overcome skin barrier functions and increase drug delivery compared to traditional creams or ointments, particularly for compounds that are not capable of penetrating the skin due to their size or relative hydrophilicity [46]. However, the process of wound healing comprises of well-organized steps of interconnected phases that appear complex where unique cells interplay with an extracellular matrix to set up a completely different framework targeted at tissue repair and growth, as this is a major concern in the economy and therapy projected in the field of medicine [47,48]. Wound healing certainly undergoes four different stages which are inflammation, multiplication, hemostasis, and remodeling. Medication-loaded nano-carriers have been presented by scientists as a way to control active release and dermal penetration patterns of contemporary medication dispatch mechanisms [49]. This permits the medicine to be targeted to specific layers of the skin, avoiding systemic percutaneous absorption.

Cardoso et al. [50] assessed the effect of phenytoin-loaded nano-capsules and nano-emulsions *in vitro* and *in vivo* skin permeation/retention when they studied the healing process of a cutaneous wound in rats by using manufactured chitosan hydrogels. It was reported that the hydrogels exhibited a pH range of 4.9–5.6, the medication content was 0.025 % (w/w), and non-Newtonian pseudoplastic rheological activity, making them useful for skin application. When compared to hydrogels containing non-encapsulated phenytoin, hydrogels prepared by incorporating nano-capsules and nano-emulsions allowed for the better regulated release of phenytoin and skin adherence. In an experiment to examine the penetration of skin in *in vitro* studies, it was revealed that nano-encapsulation can limit the penetration of phenytoin to the part where the receptor is located, hence it poses systemic absorption danger, without affecting the effect of phenytoin in *in vivo* wound healing process of the rats. El-Aassar et al. [51] developed a wound dressing material including polygalacturonic acid (PGA), hyaluronic acid (HA), and implanted silver nanoparticles that were electrospun into a nano-fibrous mat. Furthermore, an albino rat wound was extensively assessed histopathologically *in vivo*, and the antibacterial activity of the manufactured wound dressing was tested against gram +ve and gram -ve bacteria. Using the solvent diffusion approach, polymeric nano-carriers based on chitosan–hyaluronic acid (CHA) compound sponge scaffolds loaded with Andrographolide (AND) lipid were produced. To improve the distribution to wound areas, NLC4 was mixed into an acidic gel while the CHA gel was freeze-dried for 24 h to produce a CHA/NLC4 nanocomposite sponge [52]. With increased swelling, the nanocomposites also displayed a porosity of 56.22 %.

After 21 d, chitosan–hyaluronic acid/NLC4 sponge improves curing of the wound healing without defacement with no scar and enhanced tissue peculiarity in rats. Pereira and colleagues [53] also used the cationic lipid dioctadecyldimethylammonium bromide (DODMA), lecithin, and hyaluronic acid to design polysaccharide coated nanoparticles loaded with vitamin E. As a new treatment for skin wounds, these nanoparticles (diameter 130-350 nm, > 99 percent Vitamin E encapsulation effectiveness) were integrated with extracts from *Aloe vera* using polymeric films, hyaluronic acid, sodium alginate, polyethylene oxide (PEO), and polyvinylalcohol (PVA). The findings suggested that the presence of vitamin E acetate and *Aloe vera* bio-adhesive might present a novel approach in medication used in treating dermal lesions like burns. The nanoparticle-loaded polymer films regulated vitamin dissemination and lowered the rate of water loss through the injured dermal layer; these are both regarded as key aspects for improving wound healing and skin regeneration.

Neurodegenerative Disorders (NDD)

Neurodegenerative disorders (NDD) are a growing burden on healthcare systems and the most known happen to be Alzheimer's and Parkinson's disease (PD)/(AD). Aside from the complexities of these diseases' pathophysiology, NDD and AD are also particularly difficult to treat due to the blood-brain barrier's (BBB) limited permeability [54]. Although there are a limited number of medications available for the treatment of Alzheimer's disease, they are symptomatic drugs with undesired side effects. The effective uptake of active compounds into the central nervous system (CNS) by polymer nanoparticles constitutes a new sector of nanomedicine that poses a significant challenge and could represent a landmark in the treatment of various NDD.

Rabanel et al. [55] created comb-like polymers with a variable proportion of poly(ethylene glycol)–polylactic acid. Curcumin was also encapsulated in nanoparticles to create a delivery platform for disorders involving oxidative stress in the central nervous system. The authors saw a dramatic drop in the size of PEG at 15 and 20 % w/w, indicating a change to "micelle-like" or "polymer nano-aggregate" from a particle shape that is substantially hard. As a result, solid particles have a higher diffusion rate than polymer nano-aggregate particles. Furthermore, when evaluated *in vitro* on a neural cell line, the nanoparticles showed no substantial toxicity. Also, the potential of curcumin-loaded nanoparticles to reduce stress by oxidation demonstrated an association with the design of polymer as well as the organization of the nanoparticle. Carradori et al. [56] on the other hand, created nanocarriers that interacted with $A\beta_{1-42}$ in the blood, facilitating its clearance via the "sink effect," and correcting the memory deficit seen in AD-like transgenic mice. These were obtained by surface-functionalizing biodegradable PEGylated nanoparticles with an antibody directed against amyloid-beta, $A\beta_{1-42}$. The use of anti-$A\beta_{1-42}$-functionalized nanoparticles in treating AD-like transgenic mice was effective in correcting memory defects and reduced Aβ soluble peptides significantly. It also influenced the level of oligomer in the brain and increased the Aβ levels in plasma significantly. As a result of zinc sequestration in senile plaques, zinc ions local dyshomeostasis around amyloid aggregates was pointed out in AD; while amyloid-beta (A) aggregation could result to increase in the levels of zinc which is advantageous in remedying changes arising from pathogens as a result of local zinc deficiency. Vilella et al. [57] used unique zinc nanoparticles to transfer zinc into the brain through the blood-brain barrier as a promising new target for the prevention and/or treatment of Alzheimer's disease. The assessment of synapse loss, inflammatory state, and plaque load in wild type (WT) and APP23 mice *in vivo* showed that after injection of nanoparticles chronically for 14 d, there was a considerable decrease in the dimension of the plaque and the pro-inflammatory cytokines IL-6 and IL-18 also reduced. Furthermore, elevated brain zinc levels had no deleterious behavioral consequences in APP23 mice, and therapy with g7-NP-Zn restored mice incessant movement.

Sardoiwala et al. [58] investigated the neuroprotection efficacy of a nature-inspired biocompatible polydopamine nano-carrier for metformin delivery (Met encapsulated PDANPs) by crossing the blood-brain barrier *in vitro*, 3D, and *in vivo* experimental PD models using a Parkinson's disease model. Downregulation of phospho-serine 129 (pSer129)- Syn was found to have neuroprotective properties, including reduced oxidative stress, apoptotic prevention, and anti-inflammatory properties. The neuroprotective process revealed a unique connection between the epigenetic regulator EZH2 and aggregated pSer129-Syn ubiquitination and proteasomal destruction. Sánchez-Giraldo et al. [59] prepared a nanoparticle (core-shell) that was uniquely designed for Epigallocatechin-3-gallate EGCG delivery. In this work, the authors started with mixed micelles development of the triblock copolymer Pluronic® F127 and sodium dodecyl sulfate surfactant firstly; after which it was covered using chitosan and EGCG encapsulation in i*n situ*. For nerve-like cells (NLCs) both in *in vivo* and *in vitro*, the antioxidant effect of EGCG in an oxidative stress (OS) model of PD was accessed by the nanoparticles which have been purified by ultrafiltration, having a size of about 35 nm on average, EGCG encapsulation efficiency (% EE) of 83 %, colloidal stability and a release that was well sustained in *in vitro. In vivo* investigations showed that these nanoparticles protected paraquat-exposed Drosophila melanogasters against locomotor impairment, lipid peroxidation, and life span reduction. Additionally, Del Prado-Audelo et al. [60] used the emulsification-diffusion process with Pluronic® F68 as a stabilizer to build curcumin-loaded poly-caprolactone nanoparticles for *in vitro* evaluation in MIO-M1 and SH-SY5Y cells, which are cells involved in neurological disorders. With a mean particle size of 149.0 ± 2.2 nm, the curcumin-loaded nanoparticles developed had a 96 % loading efficacy. Furthermore, the nanoparticles' *in vitro* cytotoxicity in tested cells revealed adequate biocompatibility, a high rate of internalization, and great

potential as an alternative treatment for neurological illnesses such as spinocerebellar ataxias and Parkinson's disease.

Anti-viral Drug Delivery

Viral infections are a serious global health issue, representing a leading cause of death with a negative socio-economic impact that is constantly amplified. Increased medication resistance and continual viral multiplication have prompted major research into the use of nanotechnology in antiviral therapy [61,62]. Nanomaterials have distinct physicochemical properties that have been linked to drug delivery as ideal tools for viral treatment. Niak and Raval et al. [63] created a nanoparticle carrier that was optimized for antiviral medication to improve dispersion using solvent evaporation/extraction polymeric blends of cellulose acetate butyrate (CAB) and poly(vinyl pyrrolidone) (PVP). The pH-responsive drug-loaded nanoparticles had a spherical form, with diameters and efficiency encapsulation from a range of 322 to 434 nm and 50 % to 70 %, respectively, and a gradually decreasing burst dispersal style. Yan et al. [64] investigated the potential of nanoscale polyelectrolyte (PEC) complexes made by combining negatively charged curdlan sulphate (CRDS) with positively charged chitosan in aqueous solutions. The spherical PECs with a negative zeta potential (-38 mV) were successfully loaded into zidovudine (an antiviral medicine) and showed good drug loading efficiency at a regulated pH. Besides, Russo et al. [65] developed a unique nano-particulate system based on foscarnet-chitosan nanoparticles for the delivery of foscarnet (antiviral agent for herpesvirus DNA polymerase). Lung fibroblasts (HELF) cells were examined using AD-169 strain in *in vitro* studies. Further investigations revealed that foscarnet released from nanoparticles was found to be non-toxic and retained the antiviral efficacy of the free drug. Halder et al. [66] proofed that quasi-spherical monodispersed gold nanoparticles were effective against Herpes simplex virus (HSV) infection. The efficiency of the antiviral agent showed EC_{50} of 32.3 μM in HSV-1 and 38.6 μM in HSV-2. The cytotoxicity in Vero cells was reported to be CC_{50} 972.4 μM, showing a significant reduction compared to acyclovir (CC_{50} 561.7 μM); further affirming the safe use of nanoparticles. Research conducted by Gandhi et al. [67] revealed that acyclovir-loaded Eudragit RLPO® nanoparticles generated by nanoprecipitation procedures were successful in medication dispersal in sustaining drug release for a long time with medication drug capture ranging from 53.78 ± 1.34 % to 79.34 ± 1.64 %. Moreover, Ghera et al. [68] reported that the self-organization of liquid suspension of amphiphilic cyclodextrin nanospheres with perfluoroalkyl chains could trap acyclovir when it is filled to satisfaction (40 percent), with controlled dispersal for 3 h utilizing the highly loaded approach. These results show the advantages of fluorinated chains over hydrocarbon analogues; which also confirms that bioactive molecule distribution emanating from nanoparticles originating from the self-organization of amphiphilic perfluoroalkylpropanethio-α- cyclodextrin is very possible.

Anti-Biotics Drug Delivery

Antibiotics are substances that, depending on their capacity can disrupt crucial bacterial biological processes, either halt bacteria from multiplying or kill them completely. The majority of antibiotics can be classified based on their main mode of action: (1) some act as agents that are involved in the synthesis of the cell wall and they include β-lactams and glycopeptides; (2) some others such as oxazolidinones, macrolides, aminoglycosides, and tetracyclines are agents that hinder protein synthesis; (3) another group made up of fluoroquinolones and rifampin (RIF) is obstructive agents in the synthesis of nucleic acid; (4) some other agents such sulfonamides and folic acid analogs are known to inhibit metabolic pathway; and (5) others act as agents that are known to cause damage and they include polymyxins and daptomycin [69,70]. Despite antibiotics' widespread success in modern medicine, treating bacterial infections remains a major issue, particularly given the rapid growth of antibiotic resistance. Antibiotics have traditionally been administered in systemic ways to reach widely dispersed harmful germs [71].

However, as nano-medicine progresses, new techniques to enhancing local antimicrobial medication and delivery are becoming available. The progress made in these areas not only makes it easier to employ existing antibiotics but also leads to the development of wholly new bactericidal mechanisms, which will lead to more effective local antimicrobial treatments [72]. Günday et al. [73] for example, developed ciprofloxacin-loaded poly(DL-lactide-coglycolide) nanoparticles with a continuous slow release and a high local concentration at the site of action for optimum therapy. Antibiotics delivered locally as part of electrospun scaffolds provide an effective, safe, and smart augmentation for tissue regeneration. Radovic-Moreno et al. [74] generated an enveloped medication that was pH-responsive with charge-switching surface polymer (D,L-lactic-co-glycolic acid) nanoparticles of -b-poly(L-histidine)-b-poly(ethylene glycol) (PLGA-PLH-PEG) as bacterial infection cure. The carrier nanoparticles were engineered to avoid contact that is not targeted at a pH of 7.4 but adhere strongly to bacteria in acidity. The mechanism involves the switching of surface charge of pH-sensitive nanoparticles and this happens due to selectively protonated of imidazole groups of PLH at low pH. Consequently, the efficacy loss of PLGA-PLH-PEG-encapsulated vancomycin appears to be lower when pH is lesser, where minimum inhibitory concentration expresses a 1.3-fold rise in comparison to free and PLGA-PEG encapsulated vancomycin which showed 2.0-fold and 2.3-fold respectively. The preparation of reactive oxygen species ROS-responsive material, i.e. 4-(hydroxymethyl) phenylboronic acid pinacol ester-modified α-cyclodextrin (Oxi-αCD) by Wang et al. [75] was used in the encapsulation of moxifloxacin (MXF), which led to the development of ROS-responsive MXF-containing nanoparticles (MXF/Oxi-αCD NPs). MXF/Oxi-αCD NPs

were coated with 1,2-Distearoyl-sn-glycero-3-phosphoethanolamineN-methoxy(polyethylene glycol) (DSPE-PEG) and DSPE-PEG-folic acid which enhanced the entrance of released sputum by lungs and supported the effective targeting of macrophages present in tissues that are inflamed (**Figure 4**). The freedom of MXF from Oxi-CD NPs was enhanced when 0.5 mM H_2O_2 was applied according to *in vitro* drug release tests. MXF/Oxi-CD NPs were found to have stronger antibacterial activity in comparison to MXF in an *in vitro* experiment with *Pseudomonas aeruginosa.* In a separate *in vitro* cellular investigation, folic acid-modified MXF/Oxi-αCD NPs were found to be more successful at internalizing bacteria-infected macrophages. Mouse model pulmonary infection of *P. aeruginosa* was used to examine the performance of folic acid-modified MXF/Oxi-αCD; it was reported to have been more effective when compared with MXF and non-targeted MXF/Oxi-αCD NPs.

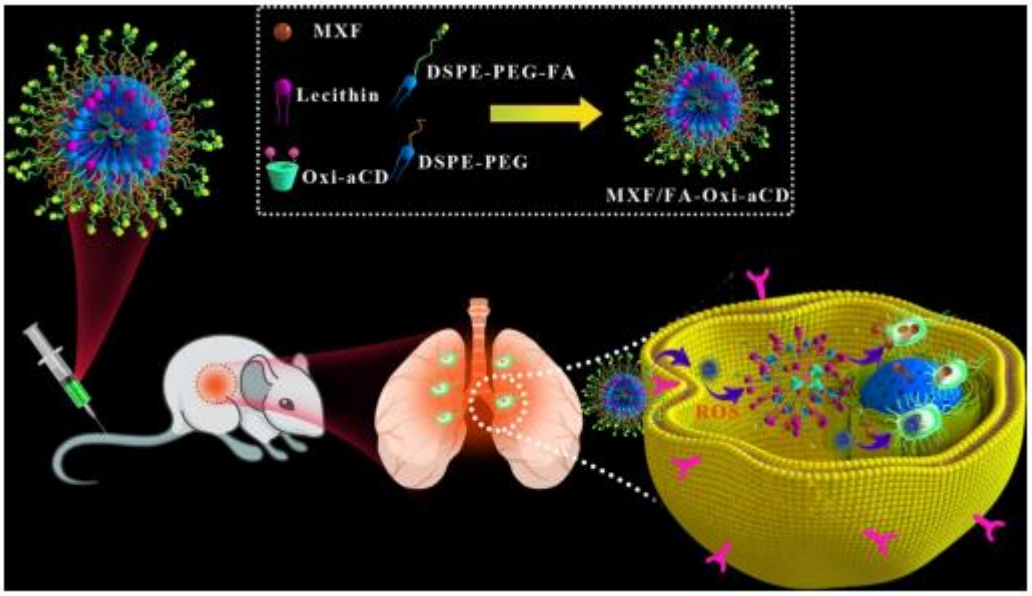


Figure 4: Schematic illustration of the fabrication of ROS responsive MXF/FA-Oxi-αCD NPs and their application for targeted treatment of pulmonary *P. aeruginosa* infection. Reproduced from [75] Copyrights Creative Common Attribution 4.0 International Version.

Conclusion

This review focuses on the most recent advances in the fabrication and application of polymer nanoparticles for drug delivery systems. Because of their small size and non-toxicity, these polymer nanoparticles can be used as nano-carriers for the site-specific/targeted delivery of drug-loaded nanoparticles with little or no associated side effects. Moreover, the nano-carriers can respond to distinct changes in a different environment, such as pH and temperature changes in biological systems. In terms of controlled release, targeted delivery, and therapeutic effect, polymer nanoparticle-based drug delivery systems have demonstrated significant advantages over traditional macro drug delivery formulations. Furthermore, they can aid in reducing dosing frequency while maintaining stability and structure.

Despite the incredible progress in designing new drug delivery agents, few challenges remain concerning nanomedicine applications, as most formulations are performed in *in-vitro* and *in-vivo* studies. Also, the commercialization of nanodrug delivery agents against drug-resistant disease-causing organisms will be beneficial in expanding the broad field of nanomedicine. Therefore, there is a need for synergistic and collaborative research among chemists, biologists, medicinal and pharmaceutical scientists, and quality control analysts to revolutionize the design of responsive polymer nanomaterials to clinically approved substances as therapeutic agents for biomedical applications to significantly improve both the quality and longevity of life.

Conflict of Interest

There is no conflict of interest to be declared by the authors.

References

1. S. Sur, A. Rathore, V. Dave, K.R. Reddy, R.S. Chouhan, V. Sadhu, Recent developments in functionalized polymer nanoparticles for efficient drug delivery system, Nano-Structures and Nano-Objects. 20 (2019) 100397. https://doi.org/10.1016/j.nanoso.2019.100397.
2. X. Dong, R.J. Mumper, Nanomedicinal strategies to treat multidrug-resistant tumors: Current progress, Nanomedicine. 5 (2010) 597–615. https://doi.org/10.2217/nnm.10.35.
3. Y. Xin, Q. Huang, J.Q. Tang, X.Y. Hou, P. Zhang, L.Z. Zhang, G. Jiang, Nanoscale drug delivery for targeted chemotherapy, Cancer Lett. 379 (2016) 24–31. https://doi.org/10.1016/j.canlet.2016.05.023.
4. D.B. Resnik, S.S. Tinkle, Ethics in nanomedicine, Nanomedicine. 2 (2007) 345–350. https://doi.org/10.2217/17435889.2.3.345.
5. N. Osman, K. Kaneko, V. Carini, I. Saleem, Carriers for the targeted delivery of aerosolized macromolecules for pulmonary pathologies, Expert Opin. Drug Deliv. 15 (2018) 821–834. https://doi.org/10.1080/17425247.2018.1502267.

G. Tiwari, R. Tiwari, S. Bannerjee, L. Bhati, S. Pandey, P. Pandey, B. Sriwastawa, Drug delivery systems: An updated review, Int. J. Pharm. Investig. 2 (2012) 2. https://doi.org/10.4103/2230-973x.96920.

6. G. Kaur, R.K. Narang, G. Rath, A.K. Goyal, Advances in pulmonary delivery of nanoparticles, Artif. Cells, Blood Substitutes, Biotechnol. 40 (2012) 75–96. https://doi.org/10.3109/10731199.2011.592494.
7. W.B. Liechty, D.R. Kryscio, B. V. Slaughter, N.A. Peppas, Polymers for Drug Delivery Systems, Annu. Rev. Chem. Biomol. Eng. 1 (2010) 149–173. https://doi.org/10.1146/annurev-chembioeng-073009-100847.
8. Komal, Sonia, S. Kukreti, M. Kaushik, Exploring the potential of environment friendly silver nanoparticles for DNA interaction: Physicochemical approach, J. Photochem. Photobiol. B Biol. 194 (2019) 158–165. https://doi.org/10.1016/j.jphotobiol.2019.03.022.
9. S. Saha, S. Ray, R. Acharya, T.K. Chatterjee, J. Chakraborty, Magnesium, zinc and calcium aluminium layered double hydroxide-drug nanohybrids: A comprehensive study, Appl. Clay Sci. 135 (2017) 493–509. https://doi.org/10.1016/j.clay.2016.09.030.
10. F. ud Din, Waqur Aman, I. Ullah, O.S. Qureshi, O. Mustapha, S. Shafique, A. Zeb, Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors, Int. J. Nanomedicine. (2017) 7291–7309. https://doi.org/10.2147/IJN.S146315.
11. M. Chamundeeswari, J. Jeslin, M.L. Verma, Nanocarriers for drug delivery applications, Environ. Chem. Lett. 17 (2019) 849–865. https://doi.org/10.1007/s10311-018-00841-1.
12. D. Lembo, M. Donalisio, A. Civra, M. Argenziano, R. Cavalli, Nanomedicine formulations for the delivery of antiviral drugs: a promising solution for the treatment of viral infections, Expert Opin. Drug Deliv. 15 (2018) 93–114. https://doi.org/10.1080/17425247.2017.1360863.
13. Y. Mi, J. Zhao, S.S. Feng, Vitamin e TPGS prodrug micelles for hydrophilic drug delivery with neuroprotective effects, Int. J. Pharm. 438 (2012) 98–106. https://doi.org/10.1016/j.ijpharm.2012.08.038.
14. S.J. Tabatabaei Rezaei, M.R. Nabid, H. Niknejad, A.A. Entezami, Multifunctional and thermoresponsive unimolecular micelles for tumor-targeted delivery and site-specifically release of anticancer drugs, Polymer (Guildf). 53 (2012) 3485–3497. https://doi.org/10.1016/j.polymer.2012.05.056
15. W.Y. Qian, D.M. Sun, R.R. Zhu, X.L. Du, H. Liu, S.L. Wang, pH-sensitive strontium carbonate nanoparticles as new anticancer vehicles for controlled etoposide release, Int. J. Nanomedicine. 7 (2012) 5781–5792. https://doi.org/10.2147/IJN.S34773.
16. H. Wu, L. Zhu, V.P. Torchilin, PH-sensitive poly(histidine)-PEG/DSPE-PEG co-polymer micelles for cytosolic drug delivery, Biomaterials. 34 (2013) 1213–1222. https://doi.org/10.1016/j.biomaterials.2012.08.072.
17. S. Cajot, K. Van Butsele, A. Paillard, C. Passirani, E. Garcion, J.P. Benoit, S.K. Varshney, C. Jérôme, Smart nanocarriers for pH-triggered targeting and release of hydrophobic drugs, Acta Biomater. 8 (2012) 4215–4223. https://doi.org/10.1016/j.actbio.2012.08.049.
18. D. Peer, J.M. Karp, S. Hong, O.C. Farokhzad, R. Margalit, R. Langer, 84 Nat nanotech 2007 R Langer Nanocarriers as an emerging platform for cancer therapy.pdf, Nat. Nanotechnol. 2 (2007) 751–760. https://doi.org/10.1038/nnano.2007.387.
19. C. Sarisozen, I. Vural, T. Levchenko, A.A. Hincal, V.P. Torchilin, PEG-PE-based micelles co-loaded with paclitaxel and cyclosporine A or loaded with paclitaxel and targeted by anticancer antibody overcome drug resistance in cancer cells, Drug Deliv. 19 (2012) 169–176. https://doi.org/10.3109/10717544.2012.674163.
20. W. Viricel, A. Mbarek, J. Leblond, Switchable lipids: Conformational change for fast pH-triggered cytoplasmic delivery, Angew. Chemie - Int. Ed. 54 (2015) 12743–12747. https://doi.org/10.1002/anie.201504661.
21. G. Soni, K. Kale, S. Shetty, M.K. Gupta, K.S. Yadav, Quality by design (QbD) approach in processing polymeric nanoparticles loading anticancer drugs by high pressure homogenizer, Heliyon. 6 (2020) e03846. https://doi.org/10.1016/j.heliyon.2020.e03846.
22. Y. Choi, S. Lim, H.Y. Yoon, B.S. Kim, I.C. Kwon, K. Kim, Tumor-targeting glycol chitosan nanocarriers: overcoming the challenges posed by chemotherapeutics, Expert Opin. Drug Deliv. 16 (2019) 835–846. https://doi.org/10.1080/17425247.2019.1648426.
23. R. Ansari, S.M. Sadati, N. Mozafari, H. Ashrafi, A. Azadi, Carbohydrate polymer-based nanoparticle application in drug delivery for CNS-related disorders, Eur. Polym. J. 128 (2020). https://doi.org/10.1016/j.eurpolymj.2020.109607.
24. M. Gagliardi, G. Bardi, A. Bifone, Polymeric nanocarriers for controlled and enhanced delivery of therapeutic agents to the CNS, Ther. Deliv. 3 (2012) 875–887. https://doi.org/10.4155/tde.12.55.
25. B. Bakan, S. Gülcemal, S. Akgöl, P.H.M. Hoet, N.Ü. Karabay Yavaşoğlu, Synthesis, characterization and toxicity assessment of a new polymeric nanoparticle, L-glutamic acid-g-p(HEMA), Chem. Biol. Interact. 315 (2020). https://doi.org/10.1016/j.cbi.2019.108870.
26. W.N. Abdel Aziz, A. Bumajdad, F. Al Sagheer, M. Madkour, Selective synthesis and characterization of iron oxide nanoparticles via PVA/PVP polymer blend as structure-directing agent, Mater. Chem. Phys. 249 (2020) 122927. https://doi.org/10.1016/j.matchemphys.2020.122927.
27. E.S. Lee, J.M. Shin, S. Son, H. Ko, W. Um, S.H. Song, J.A. Lee, J.H. Park, Recent Advances in Polymeric Nanomedicines for Cancer Immunotherapy, Adv. Healthc. Mater. 8 (2019) 1–44. https://doi.org/10.1002/adhm.201801320.

29. B. Daglar, E. Ozgur, M.E. Corman, L. Uzun, G.B. Demirel, Polymeric nanocarriers for expected nanomedicine: Current challenges and future prospects, RSC Adv. 4 (2014) 48639–48659. https://doi.org/10.1039/c4ra06406b.
30. N.M. Ushakov, G.Y. Yurkov, L. V. Gorobinskii, O. V. Popkov, I.D. Kosobudskii, Nanocomposites based on the cerium oxide nanoparticles and polyethylene matrix: Syntheses and properties, Acta Mater. 56 (2008) 2336–2343. https://doi.org/10.1016/j.actamat.2008.01.019.
31. A. Fidalgo, J.P.S. Farinha, J.M.G. Martinho, L.M. Ilharco, Nanohybrid silica/polymer aerogels: The combined influence of polymer nanoparticle size and content, Mater. Des. 189 (2020) 108521. https://doi.org/10.1016/j.matdes.2020.108521.
32. P. Smyth, T.J. Gibson, G. Irvine, G. Black, D. Lavery, M. Semsarilar, C.J. Scott, E. Themistou, pH-Responsive benzaldehyde-functionalized PEG-based polymeric nanoparticles for drug delivery: Effect of preparation method on morphology, dye encapsulation and attachment, Eur. Polym. J. 124 (2020) 109471. https://doi.org/10.1016/j.eurpolymj.2019.109471.
33. N. Karimi, M. Soleiman-beigi, A. Fattahi, Co-Delivery of All-Trans-Retinoic Acid and Docetaxel in Drug Conjugated Polymeric Nanoparticles Improving Controlled Release and Anticancer Effect, Mater. Today Commun. (2020) 101280. https://doi.org/10.1016/j.mtcomm.2020.101280.
34. H. Cheng, X. Zhang, L. Qin, Y. Huo, Z. Cui, C. Liu, Y. Sun, J. Guan, S. Mao, Design of self-polymerized insulin loaded poly(n-butylcyanoacrylate) nanoparticles for tunable oral delivery, J. Control. Release. 321 (2020) 641–653. https://doi.org/10.1016/j.jconrel.2020.02.034.
35. F. Alves Batista, S. Brena Cunha Fontele, L.K. Beserra Santos, L. Alves Filgueiras, S. Quaresma Nascimento, J.M. de Castro e Sousa, J.C. Ramos Gonçalves, A. Nogueira Mendes, Synthesis, characterization of α-terpineol-loaded PMMA nanoparticles as proposed of therapy for melanoma, Mater. Today Commun. 22 (2020). https://doi.org/10.1016/j.mtcomm.2019.100762.
36. R. Sohail, S.R. Abbas, Evaluation of amygdalin-loaded alginate-chitosan nanoparticles as biocompatible drug delivery carriers for anticancerous efficacy, Int. J. Biol. Macromol. 153 (2020) 36–45. https://doi.org/10.1016/j.ijbiomac.2020.02.191.
37. S. Thakur, H. Singh, A. Singh, S. Kaur, A. Sharma, S.K. Singh, G. Kaur, S.K. Jain, Thermosensitive injectable hydrogel containing carboplatin loaded nanoparticles: A dual approach for sustained and localized delivery with improved safety and therapeutic efficacy, J. Drug Deliv. Sci. Technol. (2020) 101817. https://doi.org/10.1016/j.jddst.2020.101817.
38. S.C. Liao, C.W. Ting, W.H. Chiang, Functionalized polymeric nanogels with pH-sensitive benzoic-imine cross-linkages designed as vehicles for indocyanine green delivery, J. Colloid Interface Sci. 561 (2020) 11–22. https://doi.org/10.1016/j.jcis.2019.11.109.
39. S. Pramual, K. Lirdprapamongkol, V. Jouan-Hureaux, M. Barberi-Heyob, C. Frochot, J. Svasti, N. Niamsiri, Overcoming the diverse mechanisms of multidrug resistance in lung cancer cells by photodynamic therapy using pTHPP-loaded PLGA-lipid hybrid nanoparticles, Eur. J. Pharm. Biopharm. 149 (2020) 218–228. https://doi.org/10.1016/j.ejpb.2020.02.012.
40. J.K.W. Lam, M.Y.T. Chow, Y. Zhang, S.W.S. Leung, siRNA versus miRNA as therapeutics for gene silencing, Mol. Ther. - Nucleic Acids. 4 (2015) e252. https://doi.org/10.1038/mtna.2015.23.
41. G.J. Prud'homme, R. Draghia-Akli, Q. Wang, Plasmid-based gene therapy of diabetes mellitus, Gene Ther. 14 (2007) 553–564. https://doi.org/10.1038/sj.gt.3302907.
42. Z. Li, W. Ho, X. Bai, F. Li, Y. Chen, X.-Q. Zhang, X. Xu, Nanoparticle depots for controlled and sustained gene delivery, J. Control. Release. 322 (2020) 622–631. https://doi.org/10.1016/j.jconrel.2020.03.021.
43. H. Jia, Y. Yang, M. Li, Y. Li, X. Han, J. Li, X. Zhang, C. Fan, T. Wu, C. Cui, X. Wei, W. Liu, An inflammation self-adaptive nanocarrier for highly efficient gene therapy, Mater. Today Chem. 17 (2020) 1–8. https://doi.org/10.1016/j.mtchem.2020.100287.
44. E. Memari, A. Maghsoudi, F. Yazdian, M. Yousefi, M. Mohammadi, Synthesis of PHB-co-PEI nanoparticles as gene carriers for miR-128-encoding plasmid delivery to U87 glioblastoma cells, Colloids Surfaces A Physicochem. Eng. Asp. 599 (2020) 124898. https://doi.org/10.1016/j.colsurfa.2020.124898.
45. M. Boer, E. Duchnik, R. Maleszka, M. Marchlewicz, Structural and biophysical characteristics of human skin in maintaining proper epidermal barrier function, Postep. Dermatologii i Alergol. 33 (2016) 1–5. https://doi.org/10.5114/pdia.2015.48037.
46. A. Vogt, C. Wischke, A.T. Neffe, N. Ma, U. Alexiev, A. Lendlein, Nanocarriers for drug delivery into and through the skin — Do existing technologies match clinical challenges?, J. Control. Release. 242 (2016) 3–15. https://doi.org/10.1016/j.jconrel.2016.07.027.
47. E. Kiwanuka, J. Junker, E. Eriksson, Harnessing Growth Factors to Influence Wound Healing, Clin. Plast. Surg. 39 (2012) 239–248. https://doi.org/10.1016/j.cps.2012.04.003.
48. S.R. Goldberg, R.F. Diegelmann, Wound Healing Primer, Surg. Clin. North Am. 90 (2010) 1133–1146. https://doi.org/10.1016/j.suc.2010.08.003.
49. S.S. Guterres, M.P. Alves, A.R. Pohlmann, Polymeric Nanoparticles, Nanospheres and Nanocapsules, for Cutaneous Applications, Drug Target Insights. 2 (2007) 117739280700200. https://doi.org/10.1177/117739280700200002.
50. A.M. Cardoso, E.G. de Oliveira, K. Coradini, F.A. Bruinsmann, T. Aguirre, R. Lorenzoni, R.C.S. Barcelos, K. Roversi, D.R. Rossato, A.R. Pohlmann, S.S. Guterres, M.E. Burger, R.C.R. Beck, Chitosan hydrogels containing nanoencapsulated phenytoin for cutaneous use: Skin permeation/penetration and efficacy in wound healing, Mater. Sci. Eng. C. 96 (2019) 205–217. https://doi.org/10.1016/j.msec.2018.11.013.

51. M.R. El-Aassar, O.M. Ibrahim, M.M.G. Fouda, N.G. El-Beheri, M.M. Agwa, Wound healing of nanofiber comprising Polygalacturonic/Hyaluronic acid embedded silver nanoparticles: In-vitro and in-vivo studies, Carbohydr. Polym. 238 (2020) 116175. https://doi.org/10.1016/j.carbpol.2020.116175.
52. R.A.B. Sanad, H.M. Abdel-Bar, Chitosan–hyaluronic acid composite sponge scaffold enriched with Andrographolide-loaded lipid nanoparticles for enhanced wound healing, Carbohydr. Polym. 173 (2017) 441–450. https://doi.org/10.1016/j.carbpol.2017.05.098.
53. G.G. Pereira, C.B. Detoni, A.G. Balducci, V. Rondelli, P. Colombo, S.S. Guterres, F. Sonvico, Hyaluronate nanoparticles included in polymer films for the prolonged release of vitamin E for the management of skin wounds, Eur. J. Pharm. Sci. 83 (2016) 203–211. https://doi.org/10.1016/j.ejps.2016.01.002.
54. M.M. Patel, B.R. Goyal, S. V. Bhadada, J.S. Bhatt, A.F. Amin, Getting into the brain: Approaches to enhance brain drug delivery, CNS Drugs. 23 (2009) 35–58. https://doi.org/10.2165/0023210-200923010-00003.
55. J.M. Rabanel, J. Faivre, G.D. Paka, C. Ramassamy, P. Hildgen, X. Banquy, Effect of polymer architecture on curcumin encapsulation and release from PEGylated polymer nanoparticles: Toward a drug delivery nano-platform to the CNS, Eur. J. Pharm. Biopharm. 96 (2015) 409–420. https://doi.org/10.1016/j.ejpb.2015.09.004.
56. D. Carradori, C. Balducci, F. Re, D. Brambilla, B. Le Droumaguet, O. Flores, A. Gaudin, S. Mura, G. Forloni, L. Ordoñez-Gutierrez, F. Wandosell, M. Masserini, P. Couvreur, J. Nicolas, K. Andrieux, Antibody-functionalized polymer nanoparticle leading to memory recovery in Alzheimer's disease-like transgenic mouse model, Nanomedicine Nanotechnology, Biol. Med. 14 (2018) 609–618. https://doi.org/10.1016/j.nano.2017.12.006.
57. A. Vilella, D. Belletti, A.K. Sauer, S. Hagmeyer, T. Sarowar, M. Masoni, N. Stasiak, J.J.E. Mulvihill, B. Ruozi, F. Forni, M.A. Vandelli, G. Tosi, M. Zoli, A.M. Grabrucker, Reduced plaque size and inflammation in the APP23 mouse model for Alzheimer's disease after chronic application of polymeric nanoparticles for CNS targeted zinc delivery, J. Trace Elem. Med. Biol. 49 (2018) 210–221. https://doi.org/10.1016/j.jtemb.2017.12.006.
58. M.N. Sardoiwala, A.K. Srivastava, B. Kaundal, S. Karmakar, S.R. Choudhury, Recuperative effect of metformin loaded polydopamine nanoformulation promoting EZH2 mediated proteasomal degradation of phospho-α-synuclein in Parkinson's disease model, Nanomedicine Nanotechnology, Biol. Med. 24 (2020) 102088. https://doi.org/10.1016/j.nano.2019.102088.
59. V. Sánchez-Giraldo, Y. Monsalve, J. Palacio, M. Mendivil-Perez, L. Sierra, C. Velez-Pardo, B.L. López, M. Jiménez-Del-Rio, Role of a novel (−)-epigallocatechin-3-gallate delivery system on the prevention against oxidative stress damage in vitro and in vivo model of Parkinson's disease, J. Drug Deliv. Sci. Technol. 55 (2020) 101466. https://doi.org/10.1016/j.jddst.2019.101466.
60. M.L. Del Prado-Audelo, J.J. Magaña, B.A. Mejía-Contreras, F. V. Borbolla-Jiménez, D.M. Giraldo-Gomez, M.C. Piña-Barba, D. Quintanar-Guerrero, G. Leyva-Gómez, In vitro cell uptake evaluation of curcumin-loaded PCL/F68 nanoparticles for potential application in neuronal diseases, J. Drug Deliv. Sci. Technol. 52 (2019) 905–914. https://doi.org/10.1016/j.jddst.2019.05.042.
61. F.D. Cojocaru, D. Botezat, I. Gardikiotis, C.M. Uritu, G. Dodi, L. Trandafir, C. Rezus, E. Rezus, B.I. Tamba, C.T. Mihai, Nanomaterials designed for antiviral drug delivery transport across biological barriers, Pharmaceutics. 12 (2020) 1–34. https://doi.org/10.3390/pharmaceutics12020171.
62. C.P. Gerba, W.Q. Betancourt, Viral Aggregation: Impact on Virus Behavior in the Environment, Environ. Sci. Technol. 51 (2017) 7318–7325. https://doi.org/10.1021/acs.est.6b05835.
63. D.R. Naik, J.P. Raval, Amorphous polymeric binary blend pH-responsive nanoparticles for dissolution enhancement of antiviral drug, J. SAUDI Chem. Soc. (2012). https://doi.org/10.1016/j.jscs.2012.09.020.
64. J.K. Yan, Y.Y. Wang, W.Y. Qiu, J.Y. Wu, Construction and characterization of nanosized curdlan sulfate/chitosan polyelectrolyte complex toward drug release of zidovudine, Carbohydr. Polym. 174 (2017) 209–216. https://doi.org/10.1016/j.carbpol.2017.06.082.
65. E. Russo, N. Gaglianone, S. Baldassari, B. Parodi, S. Cafaggi, C. Zibana, M. Donalisio, V. Cagno, D. Lembo, G. Caviglioli, Preparation, characterization and in vitro antiviral activity evaluation of foscarnet-chitosan nanoparticles, Colloids Surfaces B Biointerfaces. 118 (2014) 117–125. https://doi.org/10.1016/j.colsurfb.2014.03.037.
66. A. Halder, S. Das, D. Ojha, D. Chattopadhyay, A. Mukherjee, Highly monodispersed gold nanoparticles synthesis and inhibition of herpes simplex virus infections, Mater. Sci. Eng. C. 89 (2018) 413–421. https://doi.org/10.1016/j.msec.2018.04.005.
67. A. Gandhi, S. Jana, K.K. Sen, In-vitro release of acyclovir loaded Eudragit RLPO® nanoparticles for sustained drug delivery, Int. J. Biol. Macromol. 67 (2014) 478–482. https://doi.org/10.1016/j.ijbiomac.2014.04.019.
68. B.B. Ghera, F. Perret, Y. Chevalier, H. Parrot-Lopez, Novel nanoparticles made from amphiphilic perfluoroalkyl α-cyclodextrin derivatives: Preparation, characterization and application to the transport of acyclovir, Int. J. Pharm. 375 (2009) 155–162. https://doi.org/10.1016/j.ijpharm.2009.04.004.
69. M.H. Xiong, Y. Bao, X.Z. Yang, Y.H. Zhu, J. Wang, Delivery of antibiotics with polymeric particles, Adv. Drug Deliv. Rev. 78 (2014) 63–76. https://doi.org/10.1016/j.addr.2014.02.002.
70. F.C. Tenover, Mechanisms of antimicrobial resistance in bacteria, Am. J. Infect. Control. 34 (2006). https://doi.org/10.1016/j.ajic.2006.05.219.

72. A. Masri, A. Anwar, N.A. Khan, R. Siddiqui, The use of nanomedicine for targeted therapy against bacterial infections, Antibiotics. 8 (2019) 1–12. https://doi.org/10.3390/antibiotics8040260.
73. W. Gao, Y. Chen, Y. Zhang, Q. Zhang, L. Zhang, Nanoparticle-based local antimicrobial drug delivery, Adv. Drug Deliv. Rev. 127 (2018) 46–57. https://doi.org/10.1016/j.addr.2017.09.015.
74. C. Günday, S. Anand, H.B. Gencer, S. Munafò, L. Moroni, A. Fusco, G. Donnarumma, C. Ricci, P.C. Hatir, N.G. Türeli, A.E. Türeli, C. Mota, S. Danti, Ciprofloxacin-loaded polymeric nanoparticles incorporated electrospun fibers for drug delivery in tissue engineering applications, Drug Deliv. Transl. Res. (2020). https://doi.org/10.1007/s13346-020-00736-1.
75. A.F. Radovic-Moreno, T.K. Lu, V.A. Puscasu, C.J. Yoon, R. Langer, O.C. Farokhzad, Surface charge-switching polymeric nanoparticles for bacterial cell wall-targeted delivery of antibiotics, ACS Nano. 6 (2012) 4279–4287. https://doi.org/10.1021/nn3008383.
76. Y. Wang, Q. Yuan, W. Feng, W. Pu, J. Ding, H. Zhang, X. Li, B. Yang, Q. Dai, L. Cheng, J. Wang, F. Sun, D. Zhang, Targeted delivery of antibiotics to the infected pulmonary tissues using ROS-responsive nanoparticles, J. Nanobiotechnology. 17 (2019) 1–16. https://doi.org/10.1186/s12951-019-0537-4.